Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name:	Prostate Specific Antigen (PSA) Immunoassay
Device Trade Name:	Dimension® PSA Flex® reagent cartridge
Applicants Name and Address:	Dade Behring Inc. Glasgow Business Community Route 896 Newark, DE 19714-6101
PMA Number:	P000021
Date of Panel Recommendation:	None
CDRH Decision:	Approved
Date of Notice of Approval to Applicant:	JUL 5 2001

II. INDICATIONS FOR USE

The new indication for use, which is the subject of this Premarket Approval (PMA) Application, is as follows:

The PSA method for the Dimension® clinical chemistry system with the heterogeneous immunoassay module is an in vitro diagnostic test intended to quantitatively measure prostate specific antigen (PSA) in human serum:

1. as an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men 50 years or older. Prostate biopsy is required for diagnosis of cancer.

2. as an aid in the management (monitoring) of prostate cancer patients.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

There are no known contraindications for the Dimension® PSA Flex® reagent cartridge.

For a list of other warnings and precautions, refer to the labeling.

IV. DEVICE DESCRIPTION

The Dimension® PSA Flex® reagent cartridge method is a solid phase, two-site, one-step immunoenzymetric assay designed for use on the Dimension® clinical chemistry system with Heterogeneous Immunoassay Module. The Dimension® clinical chemistry system with Heterogeneous Immunoassay Module system is a fully automated random access analyzer. Sample is incubated with chromium dioxide particles (CrO_2) coated with monoclonal antibodies specific for a PSA binding site and with conjugate reagent [β-galactosidase (β-gal) labeled monoclonal antibodies specific for a second PSA binding site] to form a particle/PSA/conjugate sandwich. Unbound conjugate and PSA are removed by magnetic separation and washing. The sandwich bound β-gal catalyzes the hydrolysis of chlorophenol red-β-d-galactopyranoside (CPRG) to chlorophenol red (CPR). The color change measured by the Dimension® system spectrophotometer at 577nm is directly proportional to the concentration of PSA present in the patient sample.

The Dimension® PSA Flex® reagent cartridge is a plastic (high density polyethylene) molded part designed to provide 8 separate wells. All 4 of the reagents required for the Dimension® PSA Flex® reagent cartridge are contained separately, within these wells. These reagents include conjugated PSA-specific immunoglobulins required for the two-site "sandwich" enzyme-immunometric assay. In addition, there are reagents for the chromogenic detection system used for this immunoassay. There are sufficient reagents for 30 tests in each Dimension® PSA Flex® reagent cartridge.

Each Dimension® PSA Flex® reagent cartridge has a barcode label that is used to automatically transfer information to the Dimension® RxL clinical chemistry system when the cartridge is loaded into the instrument. This information includes the method name, lot number, Flex® reagent cartridge sequence number and expiration date. This information is used to assure that the proper method parameters are employed and to monitor the number of tests and "on-board" age of the reagents.

V. ALTERNATIVE PRACTICES OR PROCEDURES

Several alternate practices and procedures are used by physicians for management and monitoring of patients with prostate cancer. These include, but are not necessarily limited to, the following:

- Serum levels of total acid phosphatase
- Serum levels of total alkaline phosphatase
- Serial determination of serum prostatic acid phosphatase
- Serum levels of bone alkaline phosphatase
- Digital rectal examination
- Imaging modalities such as x-ray and/or magnetic resonance
- Ultrasonography
- Lymphangiography and/or lymphadenectomy
- Prostate biopsies

These practices and procedures are used to assess possible metastasis of the prostate cancer to the regional lymph nodes or distal sites, including bone.

Alternative practices and procedure for aiding in the detection of prostate cancer include a physical examination by digital rectal examination and imaging by ultrasound. Other devices for which there is an approved PMA for measuring serum total PSA are available to aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years and older. Diagnosis of cancer is determined by prostatic biopsy.

VI. MARKETING HISTORY

The Dimension® PSA Flex® reagent cartridge for the Dimension® clinical chemistry system with Heterogeneous Module has been available in North America, South America, major European countries (France, Spain, Italy, and Germany), and Japan since 1997. The device has been limited to monitoring of prostate cancer during this time.

The Dimension® PSA Flex® reagent cartridge for the Dimension® clinical chemistry system has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

For patients previously diagnosed with prostate cancer and monitored over time, serum levels of PSA are useful when sequential values are obtained. Monitoring is typically done on a weekly or monthly basis. After complete removal of the prostate gland (radical prostatectomy), PSA levels should decline to a very low or undetectable level. A rise of the serum PSA level in prostatectomy patients indicates residual prostate tissue, recurrence or metastasis of the disease. An erroneous result by this test could adversely affect the management of a patient. A falsely low result may delay beneficial treatment in cases of recurring or progressing cancer. A falsely elevated PSA result may trigger further investigation by alternate procedures and could lead to needless therapy. Normal physiological variation of PSA values has been reported to be less than 10% for sequential samples over a 30-day period.

For the detection of prostate cancer, serum levels of PSA are used along with digital rectal examinations (DRE) and ultrasound guided biopsy. A low level of PSA does not necessarily indicate the absence of prostate cancer. Subjects with falsely negative PSA results may not receive a necessary biopsy. Conversely, patients with non-malignant prostate disease may have abnormally elevated serum levels in the range observed for patients with prostate cancer. Subjects with falsely elevated PSA may receive unnecessary biopsies. Therefore, PSA levels should be used in conjunction with information from clinical evaluation and results from alternate procedures.

There are no significant adverse effects on the health of patients when this device is used as indicated.

VIII. SUMMARY OF STUDIES

NON-CLINICAL STUDIES

The Pre-Clinical laboratory studies performed on the Dimension® PSA Flex® reagent cartridge device were initially demonstrated in the original 510(k) Notification, K973101. For the new Intended Use, effectiveness data is in the Clinical Studies Section.

CLINICAL STUDIES

Clinical Study Objectives

A clinical study was conducted to evaluate the safety and effectiveness of the device, when used in conjunction with DRE to aid in the detection of prostate cancer in men aged 50 years or older:

1. To assess the clinical validity of PSA as measured by the device alone and in conjunction with a DRE result by determining estimates of sensitivity and specificity.

2. To assess the clinical reliability by determining estimates of the positive predictive power of PSA to detect prostate cancer as measured by the device alone and in conjunction with DRE result. In addition, the added value of PSA over DRE alone will be assessed.

Study Design

Inclusion criteria for the study were men aged fifty (50) years or older, regardless of race, who were referred to a urologist for determination of the presence of prostate cancer, without history of treatment for benign prostate disease six months prior to the referral, and without history of an evaluation for prostate cancer prior to the referral.

Exclusion criteria included men younger than fifty (50), men 50 years or older with a prior history of or treatment for prostate cancer, or men 50 years or older with a history of treatment for benign prostatic disease less than 6 months prior to the referral. In addition, men who had undergone a DRE examination or other forms of prostate manipulation less than 5 days prior to the sample blood draw were excluded.

Patient were prospectively enrolled and samples were stored from forty (40) sites throughout the United States. Six hundred and ninety-nine (699) samples were randomly selected from the larger cohort of banked samples and analyzed. These 699 samples represented thirty eight (38) of the forty (40) sites. All of these samples were collected under an IRB approved protocol and with patient informed consent. Data on each subject includes demographics and clinical history.

Outcome measures

Clinical diagnosis was based on biopsy of the prostate. The results of DRE and PSA testing were compared to the clinical diagnosis. Clinical sensitivity, specificity, and positive predictive values for PSA and DRE, alone and separately, were calculated.

Demographic Summary

Data on all of the subjects include complete demographics and clinical history including DRE, serum PSA, and biopsy. Eighty-three percent (83%) of the cohort were Caucasian, 14% were Black non-Hispanic, 3% Hispanic, and less than one percent (<1%) other racial backgrounds. Three percent (3%) had unknown race. The mean age at each site ranged from 62 to 72, with an overall mean of 66 years. One-way analysis of variance by site indicated significant differences ($p < 0.001$).

The following table summarizes the number of subjects and percentage of all subjects with each biopsy result:

Biopsy result	count	percentage
Normal	185	26.5%
BPH	128	18.3%
Prostatitis	112	16.0%
Malignant	237	33.9%
PIN/Suspic	37	5.3%
Total	699	100.0%

Poolability Analysis

The malignancy rate at each site ranged from 0% to 66.7%. The overall malignancy rate was 33.9%. A chi-square analysis indicated no significant difference in malignancy rate by site.

Analysis of variance of the mean PSA value by site indicated no significant differences. The mean PSA value for all subjects was 9.76 ng/ml (95% confidence interval 8.78 to 10.73 ng/ml, median 6.8 ng/ml).

Analysis of mean age by site indicated a significant difference while cancer prevalence and mean PSA indicated no differences by site. The similarity of cancer prevalence and mean PSA by site indicate properties of patients as enrolled at each site.

For the analysis of diagnostic test performance, the Odds ratio of cancer given an elevated PSA or abnormal DRE and the odds ratio of elevated PSA given an abnormal DRE result across all sites calculates the overall odds ratio across sites and homogeneity of odds ratio across sites. These three odds ratios and the probability of homogeneous odds ratio across sites form the basis for poolability of results across sites.

The Odds ratio of cancer given an elevated PSA result was calculated for each site. The mean odds ratio for all sites and the homogeneity of odds ratios across sites was calculated. The minimum Odds ratio was 0.173. The maximum Odds ratio was 7.857. The overall Odds ratio was 1.580 (95% confidence interval 1.001 to 2.492). The Odds ratio of cancer given an elevated PSA for pooled data was 2.299. The probability of homogeneous Odds ratios across sites was not significant.

The Odds ratio of cancer given an abnormal DRE result was calculated for each site. The minimum Odds ratio was 0.067. The maximum Odds ratio was 18.6. The overall Odds ratio was 2.223 (95% confidence interval 1.520 to 3.251). The Odds ratio of cancer given an abnormal DRE for pooled data was 1.869. The probability of homogeneous Odds ratios across sites was not significant.

The Odds ratio of an elevated PSA given an abnormal DRE result was calculated for each site. The minimum Odds ratio was 0.067. The maximum Odds ratio was 10.0. The overall Odds ratio was 0.661 (95% confidence interval 0.427 to 1.024). The Odds ratio of an elevated PSA given an abnormal DRE for pooled data was 0.675. The probability of homogeneous Odds ratios across sites was not significant.

All three analyses indicated that the odds ratios for diagnostic test performance were homogeneous across sites. In addition, the cancer prevalence and mean PSA by sites were not significantly different. Only mean age by clinical site was significantly different. Thus, 5 of 6 analyses indicate that the results across all sites are not significantly different. These results indicate that the results from all sites can be pooled together for a final analysis of the association of various variables with disease status, clinical sensitivity and specificity, and receiver-operator curve (ROC) characteristics.

Pooled Data Analysis and Results

Distribution of DRE results

A total of 699 enrolled male subjects were tested by DRE and serum PSA using the Dimension® PSA Flex® reagent cartridge. Based on DRE results, 48% of the population was considered normal, 23% not suspicious for prostate cancer, 18% suspicious of cancer, and 11 % "other". The "other" category consisted of physician statements concerning prostate size and shape.

For further analysis, the four DRE categories were collapsed into two categories of "Not Suspicious for Prostate Cancer" and "Suspicious for Prostate Cancer". The "Not Suspicious for Prostate Cancer" contains both the original "Not Suspicious for Prostate Cancer" and "Normal" categories. The "Suspicious for Prostate Cancer" contains both the original "Suspicious for Prostate Cancer" and "Other" categories. These categories were compared versus the biopsy results. Seventy-five percent (75%) of the benign biopsy results did not have suspicious digital rectal exams. Sixty-two percent (62%) of the malignant biopsies had DRE results that were not

suspicious for prostate cancer. The complete results of the distribution of DRE across the biopsy result are demonstrated in the table below.

Distribution of Digital Rectal Examination Result
Across Biopsy Result

	Biopsy-Results		
Digital-Rectal Examination Result	Benign	Malignant	Total
Not Suspicious for Cancer (DRE -)	348 75.3 %	147 62.0%	495 70.8%
Suspicious for Cancer (DRE +)	114 24.7%	90 38.0%	204 29.2%
Total	462	237	699

For the 204 of 699 subjects (29.2%) who are DRE abnormal, the probability of no association of DRE result with biopsy result was 0.0003. Thus, DRE result was significantly associated with biopsy result. The positive predictive value of DRE, 0.441 ± 0.035, was significantly greater ($p = 0.0003$) than the overall cancer prevalence (0.339 ± 0.018). This result indicates that DRE result diagnosed prostate cancer when categorized in this fashion.

Mean PSA results and Distribution

Parametric analysis (ANOVA) was performed to determine differences in mean values of PSA for the prostate cancer and benign prostate disease groups. The table below demonstrates the mean values in each of these groups.

Mean PSA Values (in ng/ml) By Digital Rectal Examination Result And Biopsy Result

	Mean PSA (ng/ml)		Std. Error (ng/ml)		95% Confidence Interval (range in ng/ml)	
	Biopsy Results		Biopsy Results		Biopsy Results	
DRE Result	Benign	Malignant	Benign	Malignant	Benign	Malignant
Not Suspicious for Cancer (DRE-)	7.76	11.92	0.67	1.03	6.45-9.08	9.90-13.94
Suspicious for Cancer (DRE+)	7.34	17.04	1.17	1.33	5.04-9.62	14.41-19.62

Note that DRE abnormal cancer subjects have significantly higher mean PSA values than DRE normal cancer subjects ($p = 0.023$). Note also that cancer subjects have significantly higher mean PSA values than non-malignant subjects ($p = 0.0007$). It is

particularly important that the mean PSA values for cancer subjects (14.20 ± 1.32 ng/ml) is significantly higher than the mean value for non-malignant subjects (8.48 ± 1.02 ng/ml). The utility of PSA in the diagnosis of prostate cancer would require that mean PSA values for cancer subjects to be significantly different from mean values for non-cancer subjects.

Parametric ANOVA analysis analyzed the differences in mean PSA of cancer subjects versus non-cancer subjects in relation to DRE status (abnormal or normal) and age. Age, DRE result (2 categories), and biopsy result (2 categories) were statistically significant contributors to the variation in PSA value. This analysis indicates an association of age, DRE result, and biopsy result with PSA value.

Subject count of PSA and DRE diagnostic test combinations

A total of 629 men were found to have an abnormal DRE or PSA result greater than 4.0 ng/mL. Biopsies were performed for all 699 men, including those without a suspicious DRE or PSA result. Of the 699 biopsied men, 237 men (33.9%) were found to have prostate cancer. T he results can be summarized in table below.

	Biopsy Result		
	Benign	Malignant	Total
PSA > 4.0, DRE-	290	135	425
PSA > 4.0, DRE +	84	80	164
Total	374	215	589
PSA ≤ 4.0, DRE-	58	12	70
PSA ≤ 4.0, DRE +	30	10	40
Total	88	22	110

Positive Predictive Power

Positive predictive power was estimated as the probability of having a positive biopsy given that the PSA value is above the cutoff. The prevalence of prostate cancer in the population was estimated to be 0.339 (95% confidence interval 0.304 - 0.374). The positive predictive power of PSA was 0.365 ± 0.020. The hypothesis that the positive predictive value equals the overall prevalence was rejected ($p < 0.0001$).

For DRE alone, the positive predictive power was 0.441 ± 0.035. The hypothesis that the positive predictive value equals the cancer prevalence was rejected ($p < 0.0001$).

For the combined use of PSA and DRE (when both are positive), the positive predictive value was 0.488 ± 0.039. The hypothesis that the positive predictive value equals the cancer prevalence was rejected ($p < 0.0001$). In addition, the hypothesis

that the positive predictive value of the combined use of PSA and DRE equals the positive predictive value of DRE alone was rejected ($p = 0.007$).

Positive predictive value	value estimate ± standard error
PSA	0.365 ± 0.020
DRE	0.441 ± 0.035
PSA > 4.0 and DRE +	0.488 ± 0.039
PSA > 4.0 and DRE -	0.318 ± 0.023
PSA < 4.0 and DRE +	0.250 ± 0.068

Thus, the positive predictive values of PSA alone, DRE alone, and PSA in conjunction with DRE (when both are positive) were significantly higher than the overall cancer prevalence. The positive predictive value of PSA in conjunction with DRE was significantly higher than the positive predictive value of DRE alone. These results support a hypothesis that PSA adds additional cancer detecting ability to DRE.

PSA and DRE as a parallel Test

PSA and Digital Rectal Examination were also analyzed as a parallel test. The parallel test was defined by the sponsor as:

- The test is positive if the DRE result is "Suspicious for Cancer" or the PSA value is 4.0 ng/mL or greater
- The test is negative otherwise.

The additional use of elevated PSA results with the normal DRE Result identified 135 additional men with prostate cancer. This increase (56.9%, 95% Confidence Interval: 50.6% to 63.3) is attributable to the utility of elevated PSA values. For the parallel test, the positive predictive power (0.358 ± 0.019) was significantly higher ($p = 0.002$) than the overall cancer prevalence. When DRE was positive and PSA was less than or equal to 4.0 ng/mL, DRE detected 10 (4.2 %) additional cancers that PSA determinations did not.

Clinical Conclusion

Results of the clinical studies using determinations of serum PSA in conjunction with DRE support the effectiveness of the Dimension® PSA Flex® reagent cartridge as an aid in the detection of prostate cancer in men aged 50 years and older in conjunction with the DRE result. The predictive power of PSA by itself (0.365) is significantly better than the cancer prevalence. For the combined use of PSA and DRE (when both are positive), the positive predictive value (0.488) was significantly higher than the

cancer prevalence. In addition, the positive predictive value of the combined use of PSA and DRE was significantly higher than the positive predictive value of DRE alone. The use of the serum PSA result along with the DRE result detected 57% more prostate cancers than cancers detected by DRE alone. The Dimension® PSA Flex® reagent cartridge assay, when used in conjunction with DRE, contributes to the detection of prostate cancer as compared to the DRE alone.

Therefore, the studies support the effective use of the device for measuring serum PSA to aid in the detection of prostate cancer in men aged 50 years and older in conjunction with DRE.

IX. CONCLUSIONS DRAWN FROM THE STUDIES

SAFETY

As a routine diagnostic test, the PSA assay involves removal of blood for testing purposes. The test, therefore, presents no more safety hazard than other tests where blood is removed from subjects.

EFFECTIVENESS

Men aged fifty (50) years or older, regardless of race, were referred to a urologist for the determination of the presence of prostate cancer. Enrolled men were without history of treatment for benign prostate disease six months prior to the referral and were without a history of an evaluation for prostate cancer prior to the referral. The current studies showed that the positive predictive values for PSA alone and in combination with DRE (i.e. when both tests are positive) detects significantly more cancer cases than the overall cancer prevalence among biopsied subjects. The positive predictive value of PSA in combination with DRE (when positive on both) is also significantly higher than the positive predictive value of DRE alone. In earlier studies of prostate cancer, digital rectal examination has been shown effective in cancer detection and has served as a more traditional cancer detection method. In the current studies, digital rectal examination also detected cancer significantly better than the overall cancer prevalence.

Among men with cancer and benign disease, PSA concentrations are higher than values in men without apparent disease. The mean PSA in cancer subjects was 14.2 ng/ml ± 1.32. At a cutoff of 4.0 ng/ml the device detects 90.7% of all cancer cases regardless of the result of the rectal examination. The mean PSA in subjects with benign disease was 8.48 ng/ml ± 1.02. At a cutoff of 4.0 ng/ml the device detects 19% of all benign cases regardless of the result of the rectal examination.

BENEFIT/RISK ANALYSIS

An elevated level of serum PSA may not necessarily indicate the presence of prostate cancer (81% false positive subjects in the current studies). Subjects with falsely elevated PSA may have unnecessary biopsies. A low level of serum PSA does not necessarily indicate the absence of prostate cancer (9% false negative subjects in the current studies). Subjects with falsely negative PSA results may not have a necessary biopsy. The

physician should utilize PSA test results in conjunction with DRE, the patient's overall clinical assessment, and other diagnostic tests such as transrectal ultrasound (TRUS). Therefore, assessment of patient status should not be based exclusively on a serum PSA result. The risk of falsely identifying cancer to the risk of missing actual cancer (false positive to false negative ratio) for PSA is approximately 5:1 (8.7:1 in the current studies).

Confirmation of prostate cancer can only be determined by prostatic biopsy. However, it is estimated that the percentage of subjects falsely identified as free of cancer using prostate tissue from six cores is approximately 25% on first sampling and declines to approximately 5% on repeat biopsy one year later. Review of biopsy results usually fails to affect the missed identification, presumably because of an insufficient number of biopsy core samples in locations containing cancer tissue. Therefore the presence of elevated PSA may fail to detect prostate cancer on first biopsy sampling. Physicians and patients should keep in mind the risks of failure to detect cancer when a negative biopsy result (absence of cancer) is received.

It is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

X. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XI. CDRH DECISION

FDA issued an approval order on JUL 5 2001.

The applicant's manufacturing facility were inspected on September 20, 2000, and were found to be in compliance with the device Good Manufacturing Practice regulations.

XII. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Conditions of Approval: CDRH Approval of this PMA is subject to full compliance with the conditions described in the approval order.

Postapproval Requirements and Restrictions: See approval order.